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During the second year of our grant, we will continue the cholesterol studies, and we have a significant effort underway to correlate biological partitioning processes with chromatographic retention on a variety of stationary phases. This work should result in several significant publications during the coming year.

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Year End Report
AFOSR 91-0254
Thermodynamically Correct Bioavailability Estimations

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The goal of this research is to develop thermodynamically correct bioavailability estimations using chromatographic stationary phases as a model of the "interphase" system. It has been previously established that octanol-water partition coefficients are not thermodynamically relevant for the modeling of bioaccumulation processes (Oppenhuizen et al., *Environ. Sci. Technol.* **1988**, **22**, 286). They investigated the thermodynamic properties of the partitioning of chlorobenzenes between fish lipids and water, and showed that bioconcentration is accompanied by *positive* enthalpy and entropy changes. In contrast, the partitioning of these compounds between octanol and water is accompanied by *negative* enthalpy and by small negative or positive entropy changes. They conclude that the differences in the thermodynamic properties of these processes arise from the different structures of fish lipids and octanol, and that only under very specific conditions and only for structurally similar compounds can a relationship between octanol-water partitioning and bioaccumulation be expected.

We have spent the past seven years investigating the molecular mechanism of retention of reversed phase liquid chromatography (RPLC), and have shown that at sufficiently high bonded chain density, that partitioning of solutes to reversed phase chromatographic stationary phases match the partitioning thermodynamics between fish lipids and water measured by Oppenhuizen.

During this first year of our AFOSR support, we have made significant progress toward our goals of using our well characterized stationary phases for modeling bioaccumulation processes. Specifically, we have made advances in three areas.

First, we have spent considerable time further investigating the thermodynamics of partitioning processes of small molecules between bulk solutions and our chromatographic stationary phases. In a collaborative study with Professor Robert Kooser, Knox College, we have used electron paramagnetic resonance techniques of spin probing to show that spectroscopic evidence exists for an increase in molecular order of the bonded octadecyl phase as a function of chain density. The spin probe, DOXYL-cholestane, shows significant increase in the order parameter, S , as a function of increased surface coverage. In addition, DOXYL-cholestane undergoes a decrease in rotational freedom and an increase in rotational anisotropy as the chain density increases. This work has just been published by ANALYTICAL CHEMISTRY. We have also had two major manuscripts accepted for publication by ANALYTICAL CHEMISTRY (listed below) detailing this work and acknowledging AFOSR support. The first of these showed both chromatographic temperature studies and differential scanning calorimetry experiments investigating the role of alkyl chain bonding density on the retention mechanism of RPLC. Phase transitions of these stationary phases were observed at bonding densities greater than $2.84 \mu\text{mole/m}^2$. Thermodynamic constants for the transfer of a solute from the mobile phase to the stationary phase (ΔH° and ΔS°) were calculated for low bonding density columns, and comparison of these values to previously reported values for the partitioning of a nonpolar solute from the bulk organic liquid to water indicated that the chromatographic retention process is not well-modeled by bulk phase oil-water partitioning processes. In addition, this data showed that the entropic contribution to retention becomes more significant with respect to the enthalpic

contribution as the stationary phase bonding density is increased, providing additional support that partitioning, rather than adsorption, is the relevant model of retention. The second paper examined temperature effects over a wide range, with emphasis on the role of the mobile phase. Van't Hoff plot shapes were used to assess the retention mechanism, and the data showed evidence of the hydrophobic effect when water-rich and/or hydrogen-bonded mobile phases such as methanol/water were used. However, different van't Hoff plot shape was observed with acetonitrile/water mobile phases, indicating a change in the retention mechanism. These data showed that the hydrophobic effect, which had been previously proposed as the driving force for retention, is not a satisfactory explanation for the retention process in all RPLC systems.

We have also spent considerable time investigating the use of mobile phase additives for the purpose of increasing the stationary phase chain density *in situ*. Specifically, we have investigated the use of cholesterol as a mobile phase additive to change the thermodynamic partitioning processes of lower density stationary phases. This work may become especially important, as *commercially available* stationary phases are of sufficiently low chain density, that they do not show the appropriate thermodynamic partitioning values. We have found that low chain density stationary phases "take-up" a significant amount of cholesterol, and significantly change the chromatographic selectivity, which is a function of the thermodynamics. This work is currently being written for submission for publication.

During the second year of our grant, we will continue the cholesterol studies, and we have a significant effort underway to correlate biological partitioning processes with chromatographic retention on a variety of stationary phases. This work should result in several significant publications during the coming year.

Publications Acknowledging AFOSR Grant Support

1. "Microscopic Order as a Function of Surface Coverage in Alkyl-Modified Silicas: Spin Probe Studies", *ANAL. CHEM.*, 1992, 64, 785-789.
2. "Temperature Dependence of Retention in Reversed Phase Liquid Chromatography: Mobile Phase Effects", Lynn A. Cole and John G. Dorsey, *ANAL. CHEM.*, 1992, 64, in press.
3. "Temperature Dependence of Retention in Reversed Phase Liquid Chromatography: Stationary Phase Effects", Lynn A. Cole, John G. Dorsey and Ken A. Dill, *ANAL. CHEM.*, 1992, 64, in press.
4. "Liquid Chromatography: Theory and Methodology", John G. Dorsey, Joe P. Foley, William T. Cooper, Robert A. Barford and Howard G. Barth, "Temperature Dependence of Retention in Reversed Phase Liquid Chromatography: Mobile Phase Effects", Lynn A. Cole and John G. Dorsey, *ANAL. CHEM.*, 1992, 64, in press. Invited review for Fundamental Review issue.

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